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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/903,412	07/11/2001	Shohei Koide	109.050US1	8219

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VIKSNINS HARRIS & PADYS PLLP
P.O. BOX 111098
ST. PAUL, MN 55111-1098

EXAMINER	
WESSENDORF, TERESA D	

ART UNIT	PAPER NUMBER
1639	

DATE MAILED: 08/09/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/903,412	KOIDE, SHOHEI	
	Examiner	Art Unit	
	T. D. Wessendorf	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *5/8/2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4,7,8 and 54-63* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 4, 7-8 and 54-63* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of Claims

Claims 1, 4, 7-8 and 54-63 are pending in the application and are under examination.

Specification

The amendment to the specification made on 5/8/2006 at page 76 is objected to because it contains an embedded hyperlink and/or other form of browser-executable code. Applicants are required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Rejections - 35 USC § 112, first paragraph

A). ***New Matter Rejection***

Claims 54-63 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention, as reiterated below.

The claimed "neutral" or "positively charged amino acid residue" as recited in e.g., claim 54 and claim 57 with an open amino acid residues at positions 7, 9 or 23 is not supported in the as-filed specification. The original disclosure describes the single, species Asn or Lys. The species do not provide support for the now broad claimed neutral or positively charged amino acid residues. The as-filed specification defines Asn as neutral amino acids but does not disclose any other neutral amino acid other than Asn. Furthermore, claim 57, which do not identify any amino acid residue(s) at position 7, 9, or 23, would likewise read on any kind of residues at these positions. The as-filed specification recites only the amino acids Asp (7, 23) and Glu (9) at these positions.

Applicant states that the new limitation is supported at page 37, lines 12-24; page 38, lines 8-13; page 71, lines 13-22 and page 76, lines 6-11 of the original specification. A review of the cited section does not provide support for the now broad claimed neutral or positively charged residue. The as-filed amino acid residue does not describe, except for the single amino acid residue, Asn, any other neutral amino acid or positively charged amino acid. Furthermore, the as-filed specification at page 76 discloses that the residues at positions 7 and 23 are Asp and Glu at position 9 are highly

conserved in several organisms. These specific amino acids are responsible for the unfavorable electrostatic interactions and its mutations is where the crux of the invention resides. Accordingly, the species provided in the original specification does not provide support for the now broad claimed neutral or positively charged residue, especially in the surrounding context of Fn3.

Response to Arguments

Applicant cites page 71, lines 13-22, where the concept of substituting a neutral or positively-charged amino acid residue for at least one of the negatively-charged residues Asp 7, Asp 23 or Glu 9 of an Fn3 molecule so as to improve the stability of the molecule.

In reply, said concept is not a positive support for the numerous amino acid residues that are encompassed in a neutral or positively charged residues, absent disclosure, as filed. It does not recite the residues included or precluded by the broad claimed functional residues. The study only discloses how the repulsive interactions between the Asp 7, Asp 23 and Glu 9 can be relieved and improves the stability of the molecule. It does not recite the numerous kinds of charged residues that achieved such stability.

B). ***Written Description***

Claims 1, 8 and 54-63 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention for reasons advanced in the last Office action, 11/16/2004.

Response to Arguments

Applicant states that the specification provides structural characteristics of the claimed Fn3 molecules, including the claimed FNfn10 molecules. For example, the structure of wild-type Fn3 molecules is known. The claimed modified Fn3 molecules have a mutation of the Fn3 structure, i.e., a substitution of at least one of amino acid residues 7, 9, or 23, e.g., at least one of Asp 7, Asp 23 or Glu 9, with another amino acid residue. As such, Applicant has recited specific structural modifications of the Fn3 molecules.

In reply, as applicant states above, ***specific*** structural modifications of the Fn3 molecules are described and not the genus of the claimed any substituents, singly or in

combinations. A written description of a ***single species is not representative of the claimed genus*** of any amino acid residues.

Applicant also states that it provides functional characteristics of the claimed modified Fn3 molecules, namely, that the modified Fn3 molecules comprise a mutation that is a stabilizing mutation. A stabilizing mutation is defined in the specification at page 6, lines 20-24, has a modification or change in the amino acid sequence of the Fn3 molecule, such as a substitution of one amino acid for another that increases the melting point of the molecule by more than 0.10C as compared to a molecule that is identical except for the change.

In reply, the modification based on the melting point of the molecule by more than .10oC is not a specific description of the genus. Any change, not necessarily in the three residues, can alter a melting point of a compound. At page 6, third incomplete paragraph of the REMARKS made on 9/23/2005, applicants define said modification including modified or unusual amino acids. The as-filed specification does not recite single, unusual or modified amino acids, especially in the context of the surrounding residues of the fibronectin molecule that results in a stable fibronectin. With respect to the function of stabilizing mutation, Koide (Biochemistry) states that it is not apparent to date why the carboxyl triad of FNfn10

has been identified to be involved in important interactions. Koide further states that it is not clear why these destabilizing residues are almost completely conserved in Fn10.

Applicant asserts that the specification is in accord with the written description requirement if one of skilled in the art, guided by the specification, could avoid inoperable combinations and practice the invention without undue experimentation. The mere possibility that a claim embraces inoperable embodiments does not render it unduly broad.

In reply, the rejection is not based on the exclusion of inoperative embodiments. Rather, whether applicant is in possession of the genus at the time of the invention based on the single species of the Fn molecule. Whether this species is correlatable to any generic substitution in the molecule (such that the desired function of compound stability is obtained). As stated by Koide above, to date it is not apparent why the carboxyl triad of FNfn10 has been identified to be involved in important interactions and it is not clear why these destabilizing residues are almost completely conserved in Fn10.

The prior art at the time of the invention supports said finding. Cota (J. Mol. Biol.) at page 721, footnote, states that unless mutant studies are undertaken there is some ambiguity as to whether some residues are exchanging only through a ***global***

exchange mechanism as well as some uncertainty in the estimation of very slow exchange rates that may have a half life of many weeks in a stable protein. Cota concludes the study that "…. even within a structural family it is difficult to generalize the relative importance of specific interactions in a protein……" Cf. with the disclosure at e.g., page 76. It states ".…….it is not clear why the destabilizing residues are almost completely conserved in Fnfn10. In contrast no other FN3 domains in human fibronectin contain this carboxyl triad. The carboxyl triad of FNfn10 may be involved in important interactions ***that have not been identified to date***……." Applicant further discloses that stability measurements cannot be performed below pH 5 due to protein aggregation, the pH dependence of FNFn3 resembles that of FNfn10. FNfn3 does not contain the carboxylate triad at positions 7, 9 and 23 indicating that the destabilization of TNfn3 at neutral pH is caused by a different mechanism than that for FNfn10. Attention is also directed to applicant's previous REMARKS (page 16, paragraph one). Applicant states that the substitution of positively charged residues for other residues would not necessarily have a stabilizing effect on a protein. A change in charge of individual amino acid residues would have differing effects on proteins, all of which have unique conformational environments. Thus, this numerous unforeseen

forces would not lead a skilled artisan to the huge scope of the claimed genus drawn to any amino acid and/or positive or neutral residues.

Claims drawn to the use of known chemical compounds must have a corresponding written description only so ***specific, not generic*** as to lead one to that class of compounds (i.e., fibronectin). In re Herschler (CCPA 1979) 200 USPQ 711. Thus, at the time of filing applicants are in possession of only the species, as disclosed and not of the genus, as presently claimed.

[As stated in the last Office action, this rejection may be overcome by incorporating the limitation of claims 4 and 7 to claim 1.]

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Rejections - 35 USC § 103

Claims 1, 4, 7-8 and 54-63 are rejected under 35 U.S.C. 103(a) as being unpatentable over Koide (WO 98/56915) or Lipovsek et al (USP 6,818,418) in view of Spector et al (Biochemistry) and reiterated below.

Koide discloses at page 6, lines 12-26 a fibronectin (Fn3) polypeptide monobody comprising a plurality of Fn3 beta-strand

domain sequences that are linked to a plurality of loop region sequences. One or more of the monobody loop region sequences of the Fn3 polypeptide vary by replacement of at least two amino acids from the corresponding loop region sequences in wild-type Fn3. One or more of the loop regions of the monobody comprise amino acid residues: i) from 15 to 16 inclusive in an AB loop; ii) from 22 to 30 inclusive in a BC loop and in the other loops. Koide discloses that 17 Fn3 domains are present just in human fibronectin that provides important information on conserved residues which are often important for the stability and folding. Large variations are seen in the BC and FG loops, Example XVII, page 51. See further the Examples, specifically the Tables.

Lipovsek discloses at e.g., col. 9, line 24 up to col. 10, line 68 a human 10Fn3 sequence that can be randomized, at a minimum, at amino acids 1-9 (which includes the claim 7 and 9 positions), 44-50, 61-54, 82-94 (edges of beta sheets); 21-31 (which includes the claim 23 position), 51-56, 76-88 (CDR-like solvent-accessible loops) and other solvent-accessible loops and beta turns to evolve new or improved compound-binding proteins. The mutations change the scaffold and thereby indirectly alter loop structure(s). If this approach is taken, mutations should not saturate the sequence, but rather few mutations should be

introduced. Preferably, no more than 10 amino acid changes, and, more preferably, no more than 3 amino acid changes should be introduced to the beta-sheet sequences. (Lipovsek at col. 18, lines 34-45). Koide or Lipovsek does not teach that the regions containing e.g., amino acids 7, 9 or 23 are involved in an unfavorable electrostatic interaction, as claimed. However, Spector at page 872 states that several residues can be destabilizing in the overall stability of a small 41-resiude helical protein. Spector further discloses that position 8 of the helical protein makes a significant, unfavorable electrostatic contribution to the overall stability. Spector further teaches that replacement of this residue with Nle or adipic acid results in a more stable protein than the wild-type protein. Spector teaches at page 873 and page 879 that the results of their study suggest a general strategy for increasing the stability of a protein by minimizing unfavorable surface interactions. Many proteins contain clusters of positively or negatively charged residues and the results presented therein suggest that optimization of surface electrostatic interactions are likely to be a generally applicable strategy for enhancing protein stability. Accordingly, it would have been obvious to one having ordinary skill in the art at the time the invention was made to determine whether the amino acids in the e.g., 1-9

or 21-31 of the Fn region of Lipovsek or Koide is involved in an unfavorable electrostatic interactions as taught by Spector. Since the interactions produces instability to the helical protein hence, one would be motivated to modify these wild-type residues. The modification of these residues by any amino acid (i.e., a library, which is a collection of amino acids) is taught by e.g., Lipovsek.

Response to Arguments

Applicant acknowledges that Koide relates to Fn3 polypeptide monobodies. But assert that only mutant fbronectin molecules with reduced stability relative to wild type fibronectin are disclosed in Koide e.g., Figure 16 and Example XVII.

In reply, whether the stability is reduced is immaterial, as the compound is known and stability is still achieved. There is nothing in the claims that preclude said reduced stability. Applicant asserts that Spector does not remedy the deficiencies of Koide and Lipovsek because Spector does not teach or suggest that the regions of Fn3 containing amino acids 7, 9 or 23 are involved in an unfavorable electrostatic interaction. Spector is related to the peripheral subunit-binding domain, derived from the dihydrolipoamide acetyltransferase component of the pyruvate

dehydrogenase multienzyme complex from Bacillus stearothermophilus, not to Fn3.

In reply, applicants cannot attack the references individually when the rejection is based on the combination of references. Spector is employed not for the purpose as argued. Lipovsek and Koide teach already the Fn3 compound. Spector is employed for its teaching of stabilization of proteins by modification of the protein structure. Spector discloses that position 8 of the helical protein makes a significant, unfavorable electrostatic contribution to the overall stability. Replacement of this residue with Nle or adipic acid results in a more stable protein than the wild-type protein. Applicant's definition of a modified residue by its melting point difference of more than .01oC is taught by Spector's suggestion of a modification.

Applicant submits that the Examiner is improperly relying on an "obvious to try" standard by suggesting that the art worker could have tried each of numerous possible choices, i.e., the listing of amino acids, until the art worker possibly arrived at a successful result.

In reply, the positive recitation in the prior art of the different amino acids that can be substituted in the Fn3 structure is not obvious to try. Rather, a modification that is

obvious to do, given the positive residues that can be employed in the substitution. There is nothing in the claims that preclude any of these amino acids, including the alleged triad substitution, singly or in combination of undefined amino acids.

No claim is allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to T. D. Wessendorf whose telephone number is(571)272-0812. The examiner can normally be reached on Flexitime.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on (571)272-4517. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

T. D. Wessendorf
Primary Examiner

Art Unit 1639

tdw
August 3, 2006